

(FILE 'HOME' ENTERED AT 17:26:39 ON 21 MAY 2001)

FILE 'MEDLINE' ENTERED AT 17:26:45 ON 21 MAY 2001

L1 22797 S MULTIPLE (1W) SCLEROSIS  
L2 0 S L1 AND (B (1W) CELL (1W) DEPLETION)  
L3 5 S L1 AND CD20  
L4 0 S NELSON MB/AU  
L5 390 S NELSON M/AU  
L6 0 S L5 AND CD20  
L7 0 S L5 AND (B (1W) CELL (1W) DEPLETION)  
L8 2632 S L1 AND ANTIBODY  
L9 0 S L5 AND (B (1W) LYMPHOCYTE (1W) DEPLETION)  
L10 0 S L1 AND (B (1W) LYMPHOCYTE (1W) DEPLETION)  
L11 0 S L1 AND L5  
L12 138 S L8 AND (B (1W) LYMPHOCYTE)  
L13 5 S L12 AND DEPLETION  
L14 24854 S L1 OR EAE  
L15 3190 S L14 AND ANTIBODY  
L16 81 S L15 AND DEPLET?  
L17 0 S L14 AND RITUXIMAB  
L18 198 S RITUXIMAB  
L19 124 S L18 AND CD20  
L20 67 S L18 AND CHIMERIC

FILE 'REGISTRY' ENTERED AT 17:45:25 ON 21 MAY 2001

FILE 'HOME' ENTERED AT 17:46:56 ON 21 MAY 2001

FILE 'REGISTRY' ENTERED AT 17:49:39 ON 21 MAY 2001

L21 1 S RITUXIMAB

FILE 'CAPLUS' ENTERED AT 17:52:03 ON 21 MAY 2001

L22 77 S L21  
L23 12700 S L22 AND MS OR EAE OR SCLEROSIS  
L24 1 S L22 AND (MS OR EAE OR SCLEROSIS)

FILE 'BIOSIS' ENTERED AT 17:53:50 ON 21 MAY 2001

L25 253 S L21  
L26 0 S L25 AND (MS OR EAE OR SCLEROSIS)

FILE 'REGISTRY' ENTERED AT 17:54:22 ON 21 MAY 2001

FILE 'DRUGPAT' ENTERED AT 17:55:01 ON 21 MAY 2001

L27 37 S L21  
L28 0 S L21 AND (MS OR EAE OR SCLEROSIS)

FILE 'MEDLINE' ENTERED AT 17:55:36 ON 21 MAY 2001

L3 ANSWER 4 OF 5 MEDLINE  
 ACCESSION NUMBER: 92147284 MEDLINE  
 DOCUMENT NUMBER: 92147284 PubMed ID: 1783458  
 TITLE: Preferential reductions in lymphocyte sub-populations induced by monthly pulses of chlorambucil: studies in patients with chronic progressive **multiple sclerosis**.  
 AUTHOR: Chiappelli F; Myers L W; Ellison G W; Liao D; Fahey J L  
 CORPORATE SOURCE: Psychoneuroimmunology Program, University of California, Los Angeles 90024.  
 CONTRACT NUMBER: AI 07126 (NIAID)  
 AI 15332 (NIAID)  
 SOURCE: INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, (1991) 13 (5) 455-61.  
 Journal code: GRI; 7904799. ISSN: 0192-0561.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199203  
 ENTRY DATE: Entered STN: 19920405  
 Last Updated on STN: 19920405  
 Entered Medline: 19920317  
 AB Thirty-three patients with chronic progressive **multiple sclerosis** (MS) were assigned to intervention groups receiving monthly pulses of chlorambucil (CB) for about one year. The monthly doses ranged from 0.4 to 1.5 mg/kg. Administration of CB resulted in preferential reduction in different lymphocyte subsets which was dose- and time-dependent. The number of B-cells (CD20) decreased more rapidly than NK-cells (CD16, CD56, CD16+CD56+) or T-cell (CD3) and T-cells subsets (CD4 and CD8). At 1.2 mg/kg, CB administration resulted in a preferential drop of T-suppressor/cytotoxic cells (CD8) compared with T-helper cells (CD4), and of the less mature "virgin" CD4 cells (CD4+CD45RA+) compared with "memory" CD4 cells (CD4+CD45RA-). The expression of activation markers (transferrin receptor, CALLa, HLA-Dr and CD38[OKT10]) within CD4, CD8 or CD20 lymphocytes was not altered by CB administration. Our data, which show that CB administration results in a preferential fall in B-cell numbers, contrast with the effects of long-term administration of the related immunosuppressive drugs, azathioprine and cyclophosphamide.

L20 ANSWER 4 OF 67 MEDLINE  
 ACCESSION NUMBER: 2001194878 MEDLINE  
 DOCUMENT NUMBER: 21117639 PubMed ID: 11226006  
 TITLE: **Rituximab**: an insider's historical perspective.  
 AUTHOR: Grillo-Lopez A J  
 CORPORATE SOURCE: Medical and Regulatory Affairs Division, IDEC  
 Pharmaceuticals Corporation, San Diego, CA 92121, USA.  
 SOURCE: SEMINARS IN ONCOLOGY, (2000 Dec) 27 (6 Suppl 12) 9-16.  
 Journal code: UN5; 0420432. ISSN: 0093-7754.  
 PUB. COUNTRY: United States  
 Historical  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200104  
 ENTRY DATE: Entered STN: 20010410  
 Last Updated on STN: 20010410  
 Entered PubMed: 20010227  
 Entered Medline: 20010405

AB **Rituximab** (Rituxan; Genentech, Inc, South San Francisco, CA and IDEC Pharmaceutical Corporation, San Diego, CA) is a unique monoclonal antibody for the treatment of non-Hodgkin's lymphoma. This **chimeric** mouse/human antibody was discovered in 1991 at IDEC Pharmaceuticals' laboratories, where the antibody was genetically engineered and produced utilizing high-yield expression systems. It is a human IgG1 kappa antibody with mouse variable regions isolated from a murine anti-CD20 antibody, IDEC-2B8, that binds with high affinity to cells expressing the CD20 antigen found on the surface of malignant and normal B cells, but not on other normal tissues. It mediates complement-dependent cell lysis in the presence of human complement, and antibody-dependent cellular cytotoxicity with human effector cells. Also, it has been shown to induce apoptosis and to sensitize chemoresistant human lymphoma cell lines in vitro. Clinical development was expedited (3 years) with the first patient entered in phase I trials in March 1993 and the last patient entered in the phase III study in March 1996. IDEC Pharmaceuticals began a collaboration with Genentech, Inc in March 1995 and with F. Hoffman-LaRoche (Nutley, NJ) shortly thereafter. Marketing approval was granted by the US Food and Drug Administration on November 26, 1997 (and by the European Union on June 2, 1998) for the indication

of relapsed or refractory, CD20-positive, B-cell, low-grade or follicular non-Hodgkin's lymphoma. **Rituximab** is the first therapeutic monoclonal antibody approved for the treatment of cancer and the first single agent approved specifically for therapy for a lymphoma.

Substantial research has been performed over the past 8 years to further the understanding of this novel therapeutic. Nevertheless, much remains to be accomplished in key areas such as mechanism of action and resistance, combinations with chemotherapy, biologics and radiotherapy/radioimmunotherapy, role within multimodality regimens, and nonmalignant applications. Research conducted in the coming years should be targeted toward resolving these important issues.

L24 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS  
 ACCESSION NUMBER: 2000:814347 CAPLUS  
 DOCUMENT NUMBER: 133:361915  
 TITLE: Treatment of autoimmune diseases with antagonists  
 which bind to B cell surface markers  
 INVENTOR(S): Curd, John G.; Kunkel, Lori A.; Grillo-Lopez, Antonio  
 J.  
 PATENT ASSIGNEE(S): Genentech, Inc., USA; Idec Pharmaceuticals, Inc.  
 SOURCE: PCT Int. Appl., 34 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2000067796	A1	20001116	WO 2000-US40018	20000504
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 1999-133018	P 19990507
			US 1999-139621	P 19990617
AB The present invention concerns treatment of autoimmune diseases with antagonists, e.g. antibodies, which bind to B cell surface markers, such as CD19 or CD20.				
REFERENCE COUNT:		5		
REFERENCE(S):		(1) Johnston, P; BLOOD, PART 2 1999, V94(10, SUPP 1), P4386 (2) Lee, E; BLOOD 1998, V92(9), P3490 CAPLUS (3) Mow, B; BLOOD, PART 2 1999, V94(10, SUPP 1), P3526 (4) Scheuermann, R; US 5686072 A 1997 CAPLUS (5) Univ Leland Stanford Junior; WO 9503770 A 1995 CAPLUS		

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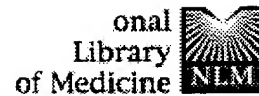
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Immunomodulatory drugs for multiple sclerosis: a systematic review of clinical and cost effectiveness.

Expert Opin Pharmacother. 2001 Apr;2(4):623-39.

PMID: 11336612 [PubMed - in process]

- ☐ 2: [O'Connor KC, Bar-Or A, Hafler DA.](#) Relate

The neuroimmunology of multiple sclerosis: possible roles of T and B lymphocytes in immunopathogenesis.

J Clin Immunol. 2001 Mar;21(2):81-92.

PMID: 11332657 [PubMed - in process]

Related Resources

- ☐ 3: [Gironi M, Bergami A, Brambilla E, Ruffini F, Furlan R, Comi G, Martino G.](#) Relate

Immunological markers in multiple sclerosis.

Neurol Sci. 2000;21(4 Suppl 2):S871-5. Review.

PMID: 11205366 [PubMed - indexed for MEDLINE]

- ☐ 4: [Berger T, Reindl M.](#) Relate

Immunopathogenic and clinical relevance of antibodies against myelin oligodendrocyte glycoprotein (MOG) in Multiple Sclerosis.

J Neural Transm Suppl. 2000;(60):351-60. Review.

PMID: 11205153 [PubMed - indexed for MEDLINE]

- ☐ 5: [Campbell JD, HayGlass KT.](#) Relate

T cell chemokine receptor expression in human Th1- and Th2-associated diseases.

Arch Immunol Ther Exp (Warsz). 2000;48(6):451-6. Review.

PMID: 11197598 [PubMed - indexed for MEDLINE]

- ☐ 6: [Donoghue S, Greenlees C.](#) Relate

Drugs in development for the treatment of multiple sclerosis: antigen non-specific therapy update.

Expert Opin Investig Drugs. 2000 Jan;9(1):167-71. Review.

PMID: 11060669 [PubMed - indexed for MEDLINE]

- ☐ 7: [Ewing C, Bernard CC.](#) Relate

Insights into the aetiology and pathogenesis of multiple sclerosis.

Immunol Cell Biol. 1998 Feb;76(1):47-54. Review.

PMID: 9553776 [PubMed - indexed for MEDLINE]

☐ 8: [Genain CP, Cannella B, Hauser SL, Raine CS.](#) Relate

Identification of autoantibodies associated with myelin damage in multiple sclerosis.

Nat Med. 1999 Feb;5(2):170-5.

PMID: 9930864 [PubMed - indexed for MEDLINE]

☐ 9: [Wekerle H.](#) Relate

Remembering MOG: autoantibody mediated demyelination in multiple sclerosis?

Nat Med. 1999 Feb;5(2):153-4. No abstract available.

PMID: 9930860 [PubMed - indexed for MEDLINE]

☐ 10: [Liblau RS, Fontaine B.](#) Relate

Recent advances in immunology in multiple sclerosis.

Curr Opin Neurol. 1998 Aug;11(4):293-8. Review.

PMID: 9725073 [PubMed - indexed for MEDLINE]

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